Malattie genetiche dei piccoli vasi

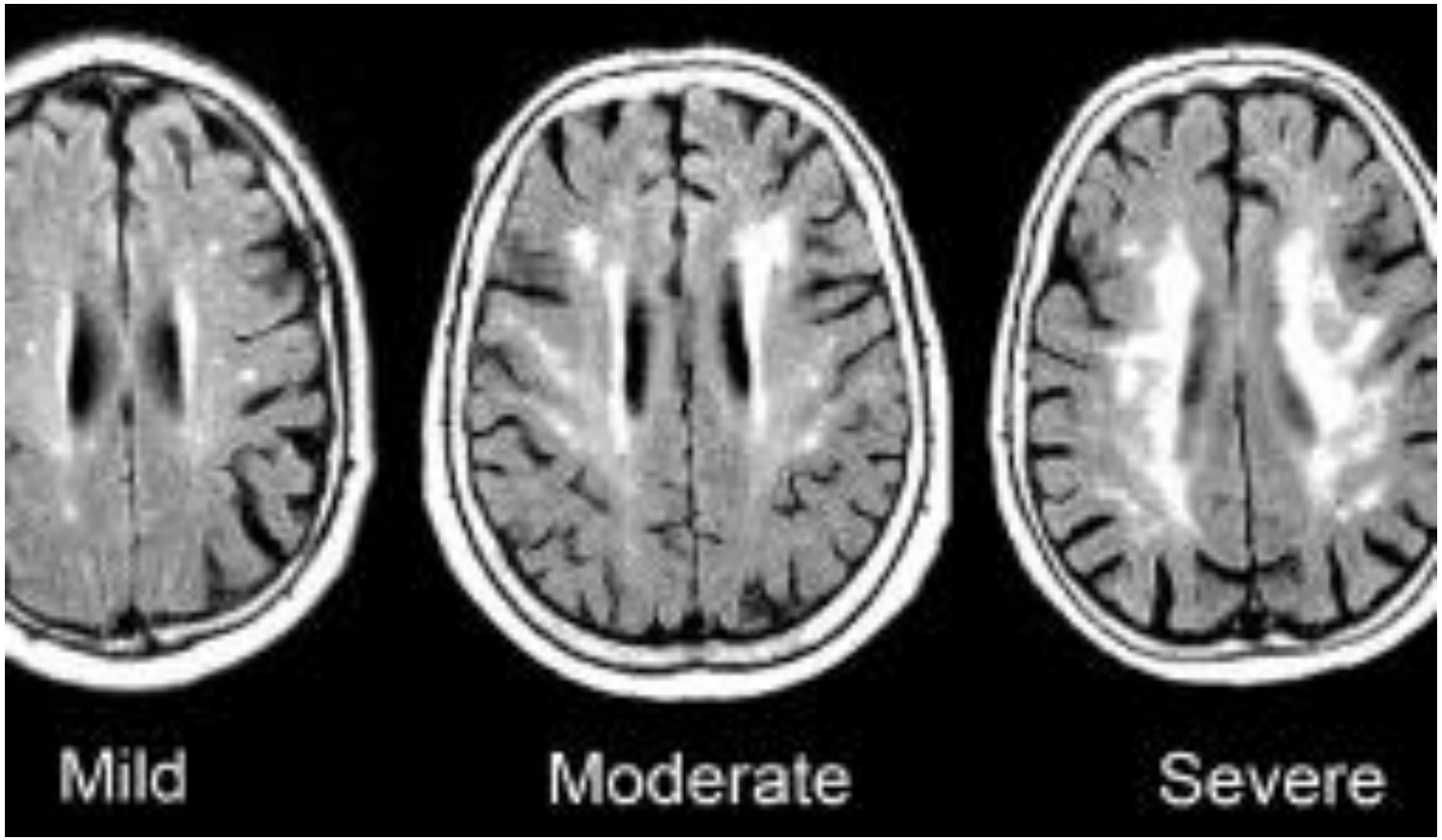
Diagnostic and Therapeutic Approaches to Monogenic SVD: Consensus Statement

Michelangelo Mancuso

University of Pisa

Sin
SOCIETÀ ITALIANA DI NEUROLOGIA

the home of neurology
ean



Cerebral small vessel diseases

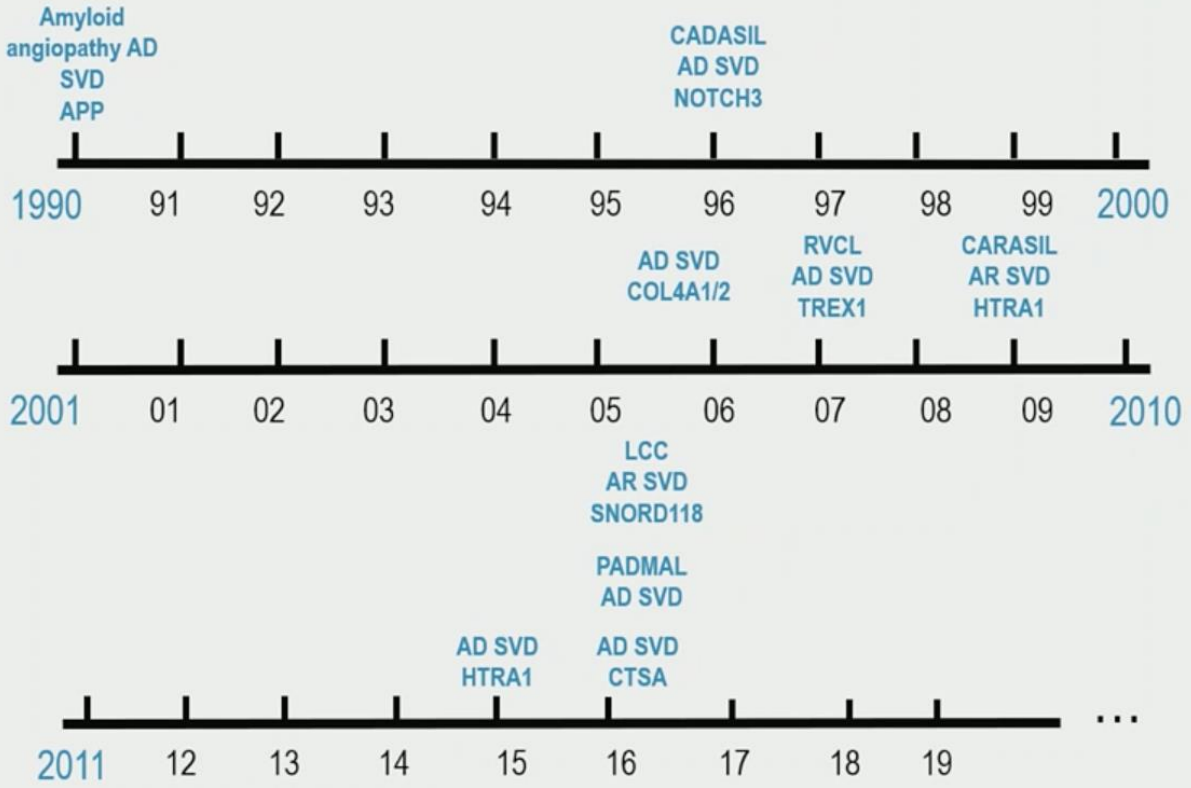
- **Cerebral small vessel disease (cSVD) is a term used for different pathological processes that affect the small vessels of the brain, including small arteries, arterioles, capillaries, and small veins**

Monogenic Cerebral Small Vessel Disease

An exciting and rapidly progressing area

- Increasing diagnosed With NGS in daily practice
- Increasing number of causes Exome sequencing
- Can be challenging to diagnose
- New diagnostic strategies
- No management guidelines

Progress in molecular deciphering of rare genetic cSVD



- But in most familial cSVD the causative gene is still not identified today
- Need to speed up the process of gene identification. Ongoing work !

EAN GUIDELINES/CME ARTICLE

Monogenic cerebral small-vessel diseases: diagnosis and therapy. Consensus recommendations of the European Academy of Neurology

M. Mancuso[a], M. Arnold[b], A. Bersano[c], A. Burlina[d], H. Chabriat[e], S. Debette[f], C. Enzinger[g], A. Federico[h], A. Filla[i], J. Finsterer[j], D. Hunt[k], S. Lesnik Oberstein[l], E. Tournier-Lasserve[m] and H. S. Markus[n]

Monogenic stroke. Diagnostic and therapeutic approach

Experts selected from the NG and Stroke Panels 2018:

M Arnold, A Bersano, A Burlina, H Chabriat, S Debette, C Enzinger, A Federico, A Filla, J Finsterer, D Hunt, S Lesnik-Oberstein, M Mancuso, HS Markus E Tournier-Lasserve

Pts advocacy groups: Lily Foundation

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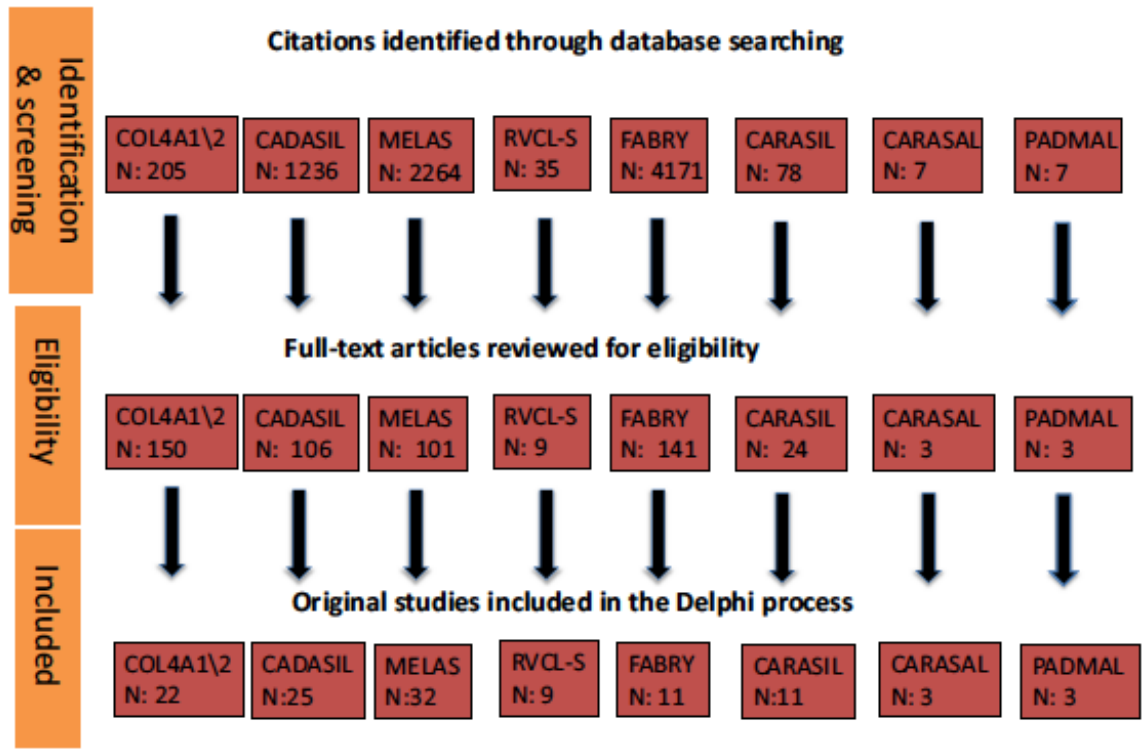
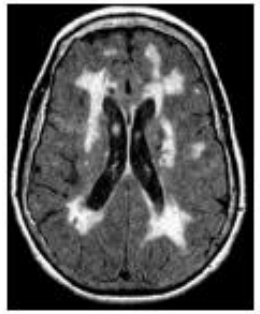


Figure 1 Comprehensive search strategy in MEDLINE database used by the different working groups.

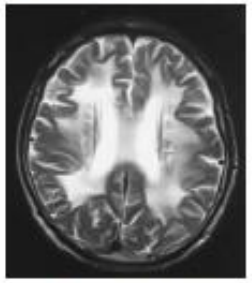
Red flags suggesting monogenic disease

	/5	%
FAMILY HISTORY	5	100
YOUNG AGE AT ONSET	4,92	100
CHARACTERISTIC NEUROIMAGING FEATURES	4,54	84,6
CONSANGUINITY	4,92	100
EXTRACEREBRAL\SYSTEMIC FEATURES	4,54	100
CLINICAL PHENOTYPE CHARACTERISTIC FOR SPECIFIC MONOGENIC DISEASE	4,61	92,8
NEGATIVE CLINICAL WORKUP FOR OTHER CAUSES OF cSVD	4,15	69,2

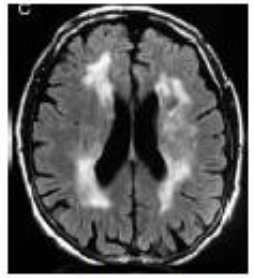
Mancuso et al, 2020



CADASIL
NOTCH 3

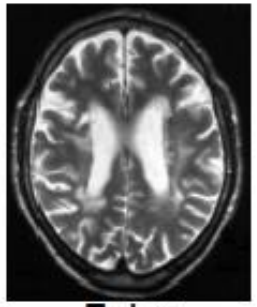


CARASIL
HTRA1

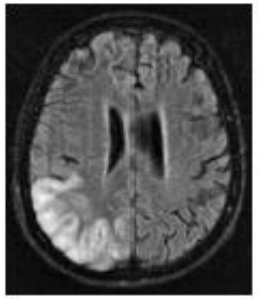


COL4A1/2

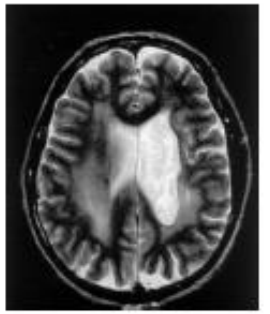
Small vessel disease



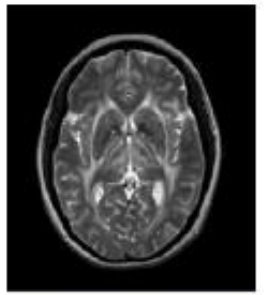
Fabry
α-galactosidase



MELAS



RVCL-S
TREX1



CARASAL
CTSA

Management recommended for all monogenic cSVD

General principles:

- Monogenic cSVD patients should be followed up by specialised centres and/or by an expert neurologist

- Genetic counselling should include discussion of family planning

- Because vascular risk factors increase the severity of CADASIL, and may well do the same for other monogenic causes of cSVD, lifestyle changes eg.smoking, healthy diet and physical exercise should be advised

- cSVD patients should have a yearly evaluation of their vascular risk factor profile, but do not need yearly MRI

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Journal of Neurology
https://doi.org/10.1007/s00415-020-09836-x

REVIEW

Heritable and non-heritable uncommon causes of stroke

A. Bersano[1] · M. Kraemer[2,3] · A. Burlina[4] · M. Mancuso[5] · J. Finsterer[6] · S. Sacco[7] · C. Salvarani[8] · L. Caputi[1] · H. Chabriat[9] · S. Lesnik Oberstein[10] · A. Federico[11] · E. Tournier Lasserve[12] · D. Hunt[13] · M. Dichgans[14] · M. Arnold[15] · S. Debette[16] · H. S. Markus[17]

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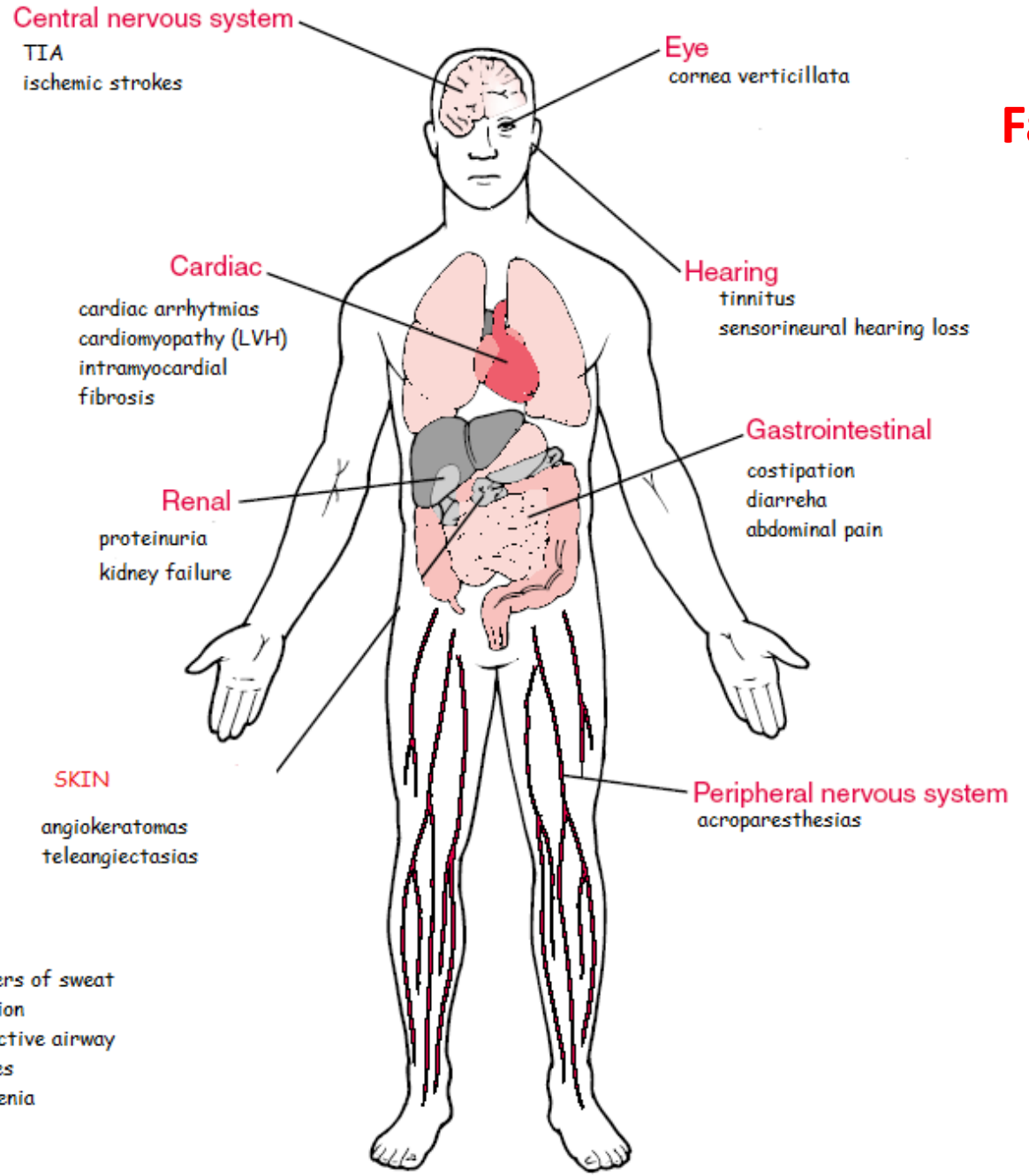
Fabry Disease



FABRY DISEASE

- Incidence: 1/40.000 male
- Deficit of α- galactosidase A
- accumulation of glycosphingolipids (globotriaosylceramide Gb3) with a progressive intracellular endotelial storage of Gb3 in various tissues and organs (renal, cardiac and CNS)

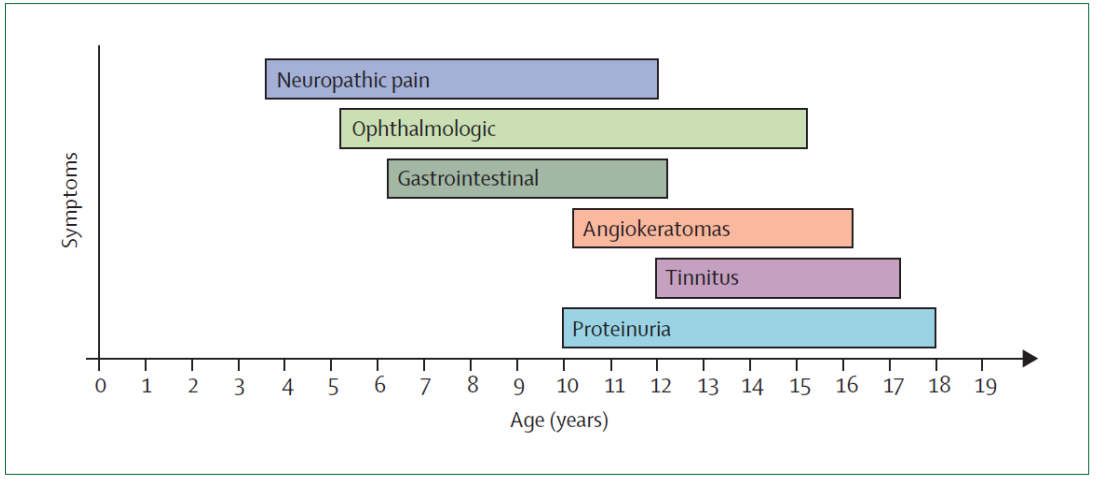


Figure 3: Ranges of age at onset of different clinical manifestations in men with Fabry's disease

Zarate 2008

CNS manifestations of Fabry's disease

Andreas Fellgiebel, Matthias J Müller, Lionel Ginsberg

Background Fabry's disease is a rare hereditary lysosomal storage disease with multiorgan involvement. Deficiency of α-galactosidase A activity leads to accumulation of neutral glycosphingolipids, especially in vascular endothelial and smooth-muscle cells. Along with progressive renal and cardiac dysfunction, stroke is a major and often life-threatening burden of the disease. Cerebral vasculopathy, confirmed by neuropathological, neuroradiological, and functional studies, occurs commonly and leads to ischaemic cerebrovascular events at an early age.

Lancet Neurol 2006; 5: 791–95

Department of Psychiatry, University of Mainz, Mainz, Germany (A Fellgiebel MD, M J Müller MD); and Department of Neurology, Royal Free Hospital, London,

Panel: Neurological features of Fabry's disease

Peripheral nervous system

Peripheral neuropathy (especially small fibre), autonomic dysfunction

Neuropathic pain

- Episodic pain crises (triggered, for example, by warming)
- Acroparaesthesiae

Impaired temperature sensation

Hypohidrosis

Intestinal dysmotility (including abdominal pain and diarrhoea)

Peripheral vasomotor dysregulation

Central nervous system

Cerebrovascular events

- ischaemic stroke
- Transient ischaemic attack

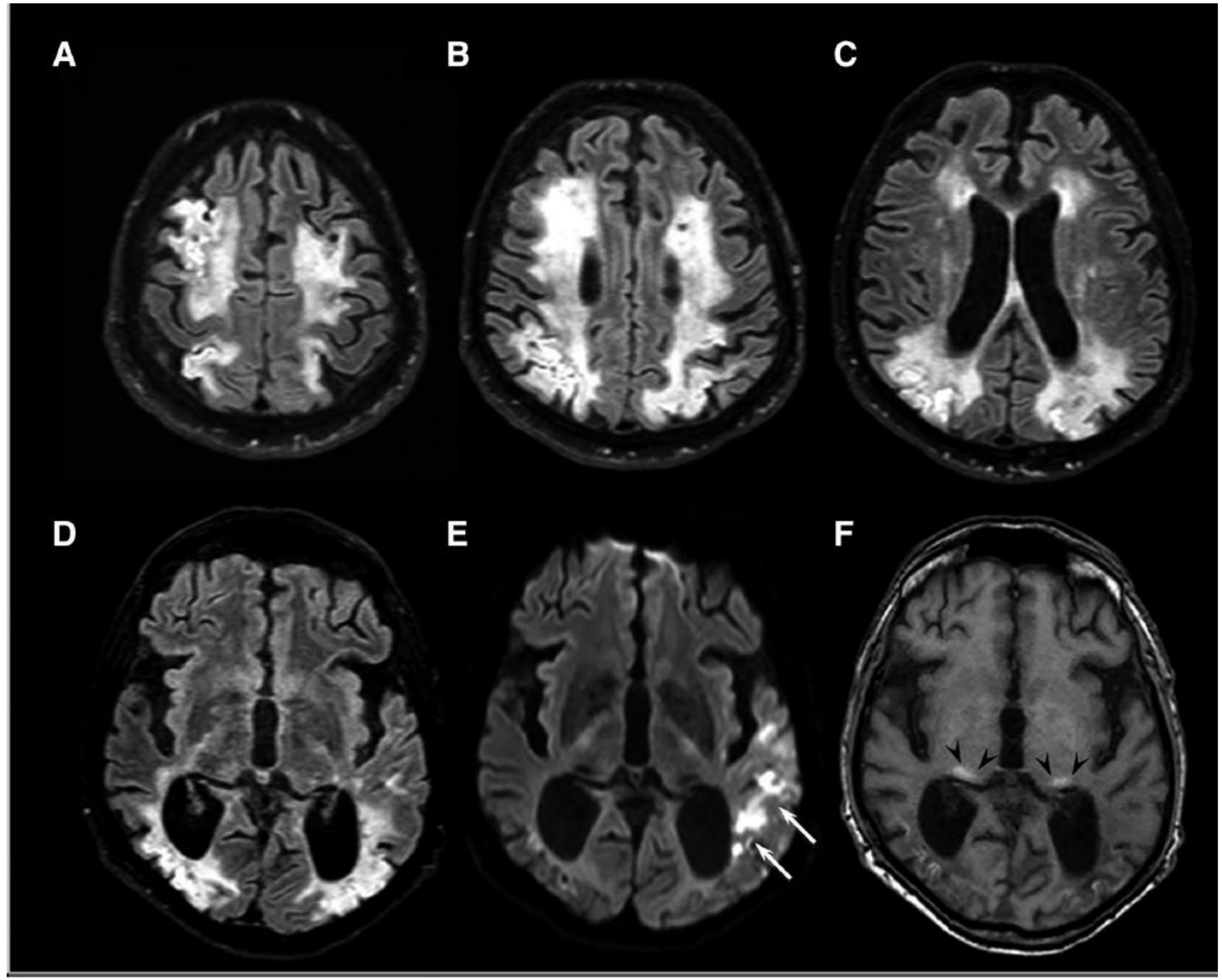
Tinnitus

Hearing impairment

Vertigo

Psychiatric disorders (especially depression)

Cognitive impairment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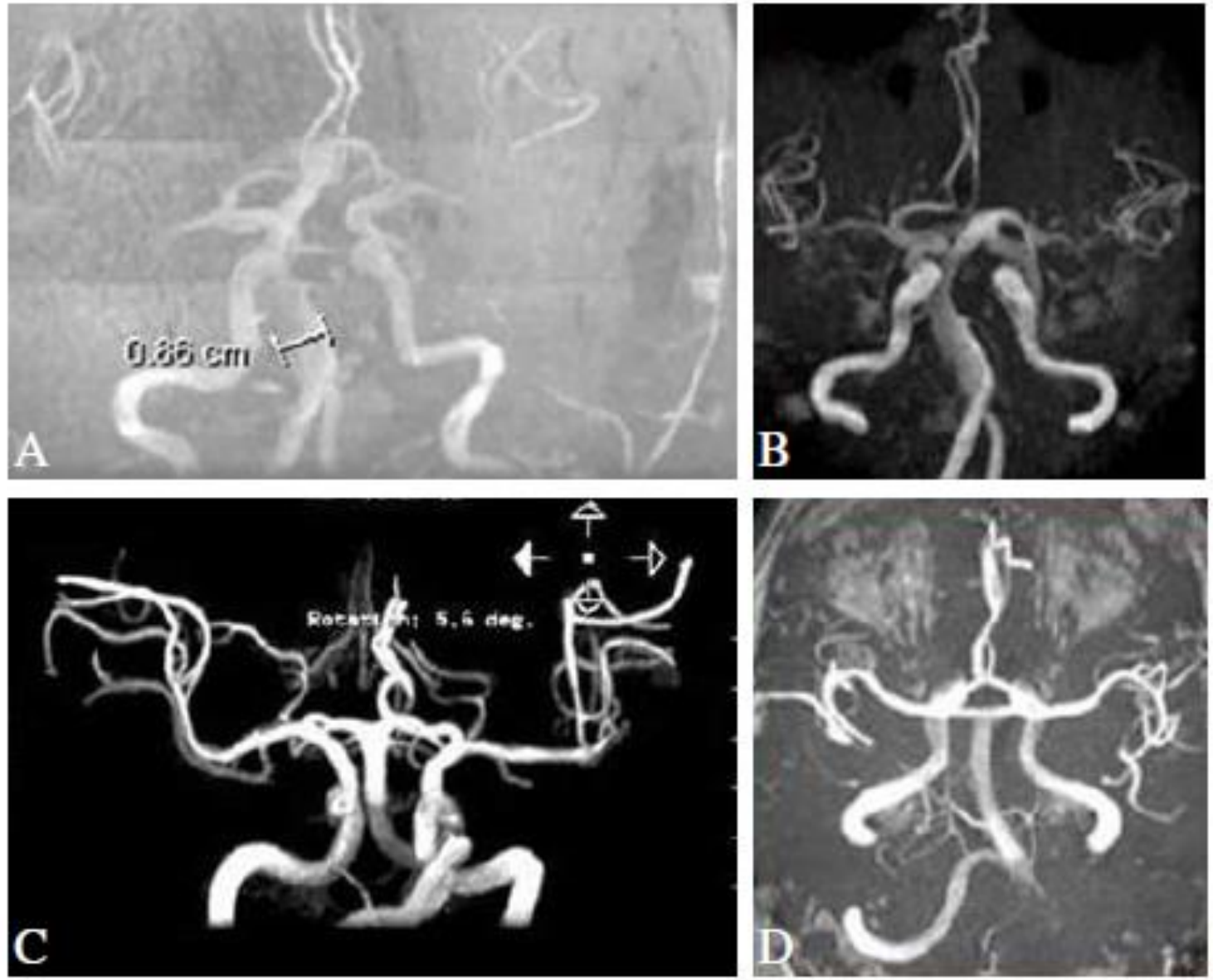
0.85 cm
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EAN Fabry disease

- Fabry disease explains less than 1% of cryptogenic ischaemic strokes in young adults
- Cognitive function has been less studied than other neurological complications in FD
- Besides symptomatic drugs, specific therapies are available

EAN Management-I

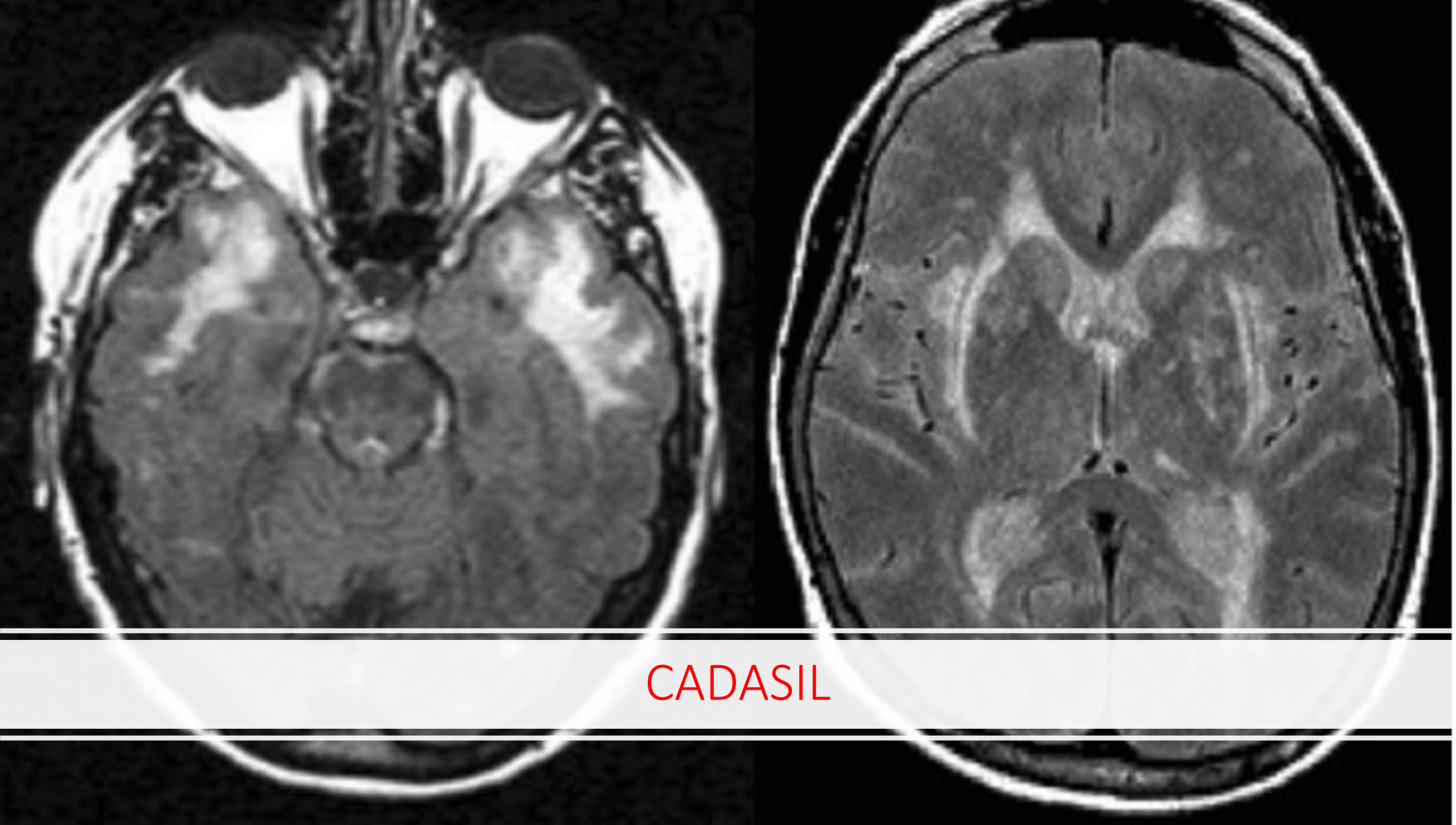
- Early diagnosis is important for the correct management of patients with FD
- Systemic thrombolysis is not contraindicated in FD
- Thrombectomy can be applied in case of proximal occlusion of cerebral arteries in patients with FD
- There is no evidence to recommend antithrombotic treatment for primary prevention for stroke in FD
- Primary stroke prevention in FD includes lifestyle modifications
- Patients with FD should receive antithrombotic therapy after the first cerebrovascular event. Regarding stroke prevention, there are no data yet on whether antithrombotic drugs are effective in FD.

Experts' recommendations include lifestyle modifications to control common risk factors and antithrombotic drugs for secondary prevention

Mancuso et al, EAN 2020

EAN Management-II

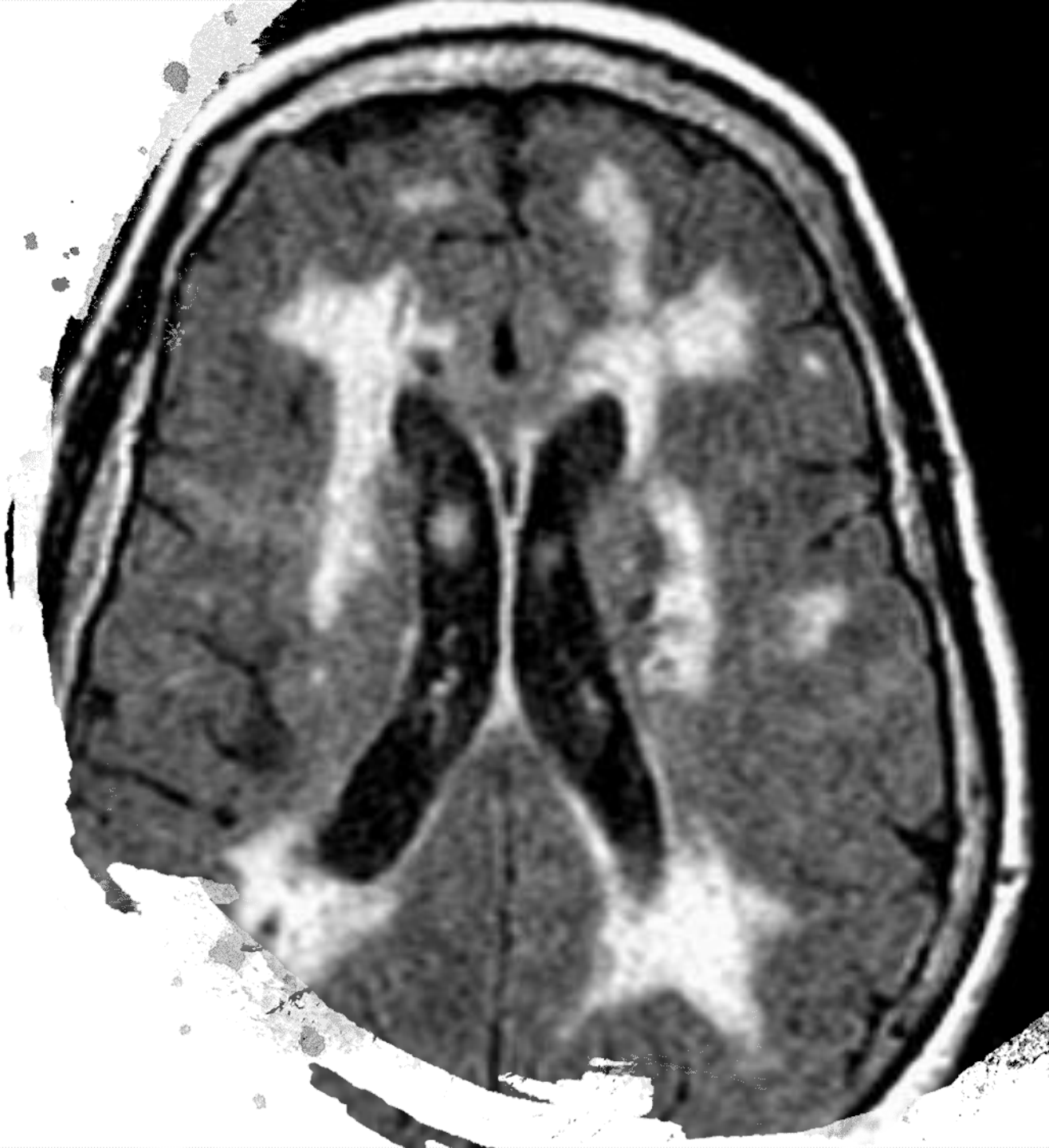
- ERT is usually recommended to reduce complications of FD although there is no good evidence that ERT can prevent stroke recurrence.
- Stroke recurrence in patients with FD, with and without ERT, has been reported. There was strong consensus that there was no clear evidence that ERT reduced stroke risk in FD. It was agreed that more data are required.
- Two recent systematic reviews reported a lower incidence of cerebrovascular events with ERT. These are based on observational data and it was agreed that more data are required, ideally from randomized trials

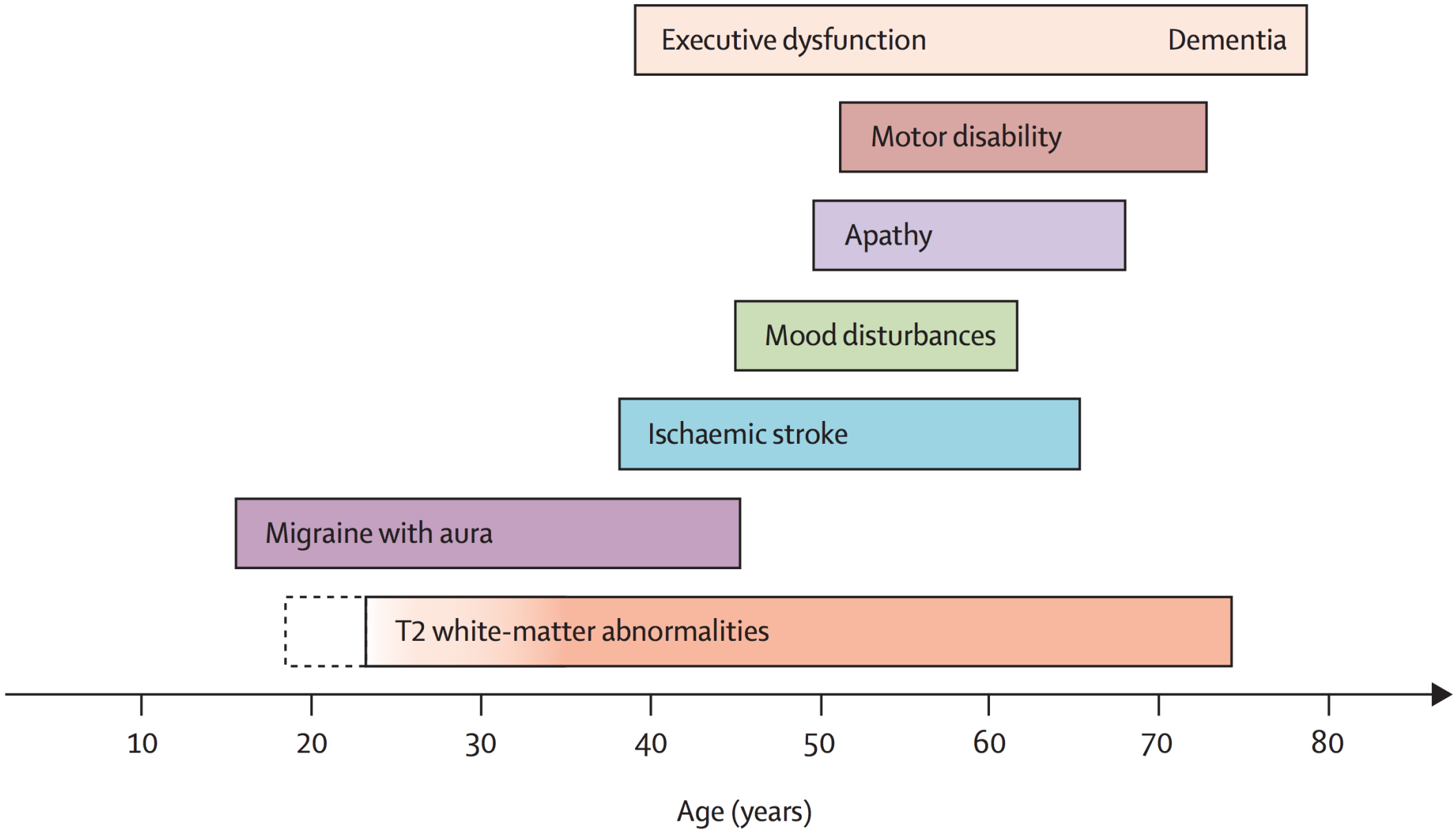


CADASIL

CADASIL

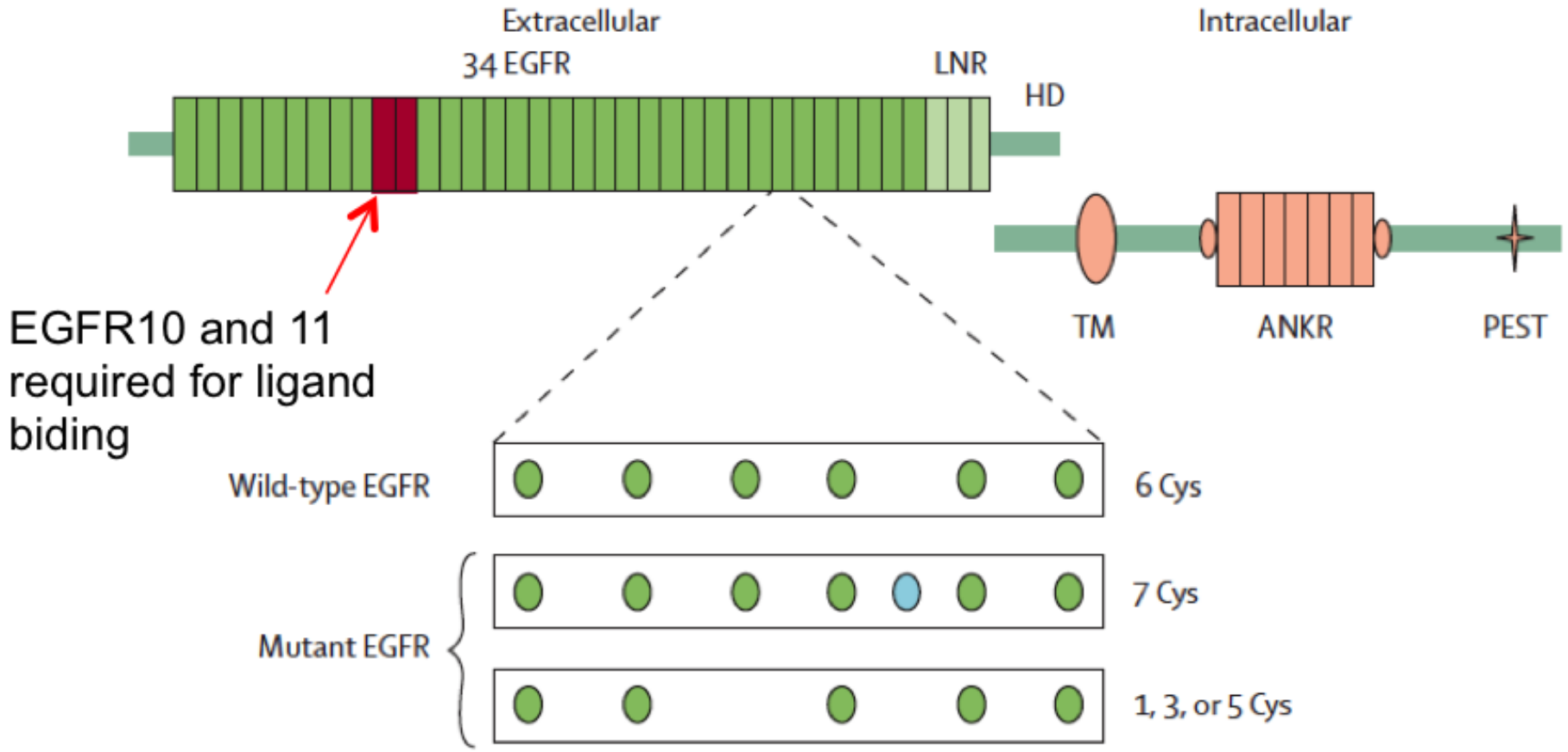
- Autosomal dominant inheritance
- Most common monogenic cSVD
- MRI -lacunar infarcts and WMH
- NOTCH3 mutations





Chabriat et el, 2009

CADASIL GENETICS



Chabriat et el, 2009

EAN recommendations

Clinical and neuroimaging diagnosis

- CADASIL can present with mild signs or symptoms, even in elderly individuals (70+ years) with a negative medical history of stroke and a negative family history
- Although most patients have a family history, if the clinical and imaging phenotype is consistent with CADASIL the diagnosis should be considered
- CADASIL cannot be ruled out in presence of common cerebrovascular risk factors and extensive WMHs
- CADASIL should be considered in the differential diagnosis of multiple sclerosis

EAN recommendations

Management

•Treat of risk factors

Good evidence for smoking and BP

•Antithrombotics

No clear evidence esp before stroke

Avoid warfarin and dual anti-platelets

•Treatment of complications

Migraine

•Conventional migraine prophylaxis

•Triptans are not contraindicated and may help

Depression

•Thrombolysis

- should not receive thrombolysis for acute ischaemic stroke unless due to a large artery occlusion secondary to a concurrent cause (which is very uncommon)

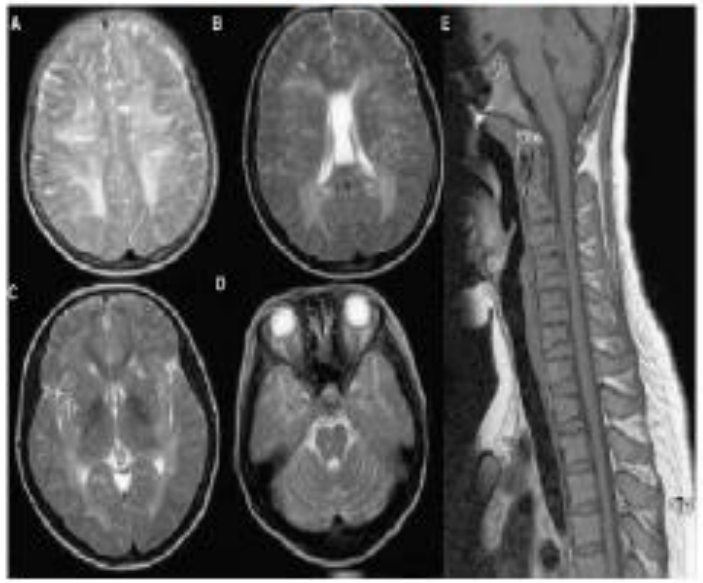
CARASIL

- Cerebral Autosomal Recessive Arteriopathy with Subcortical Infarcts and Leukoencephalopathy

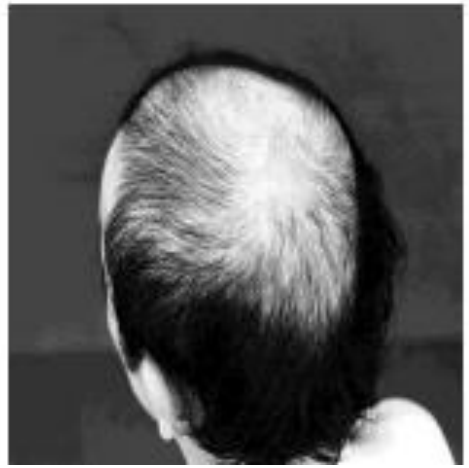
- Early-onset SVD
  - lacunar strokes,
  - vascular dementia,
  - non-neurological features e.g. alopecia, degenerative disc disease

- Mutations in HTRA1 gene lead to deficient inhibition by HtrA1 – increased TGFβ signalling

Zheng et al , 2008, J Clin Neurosci

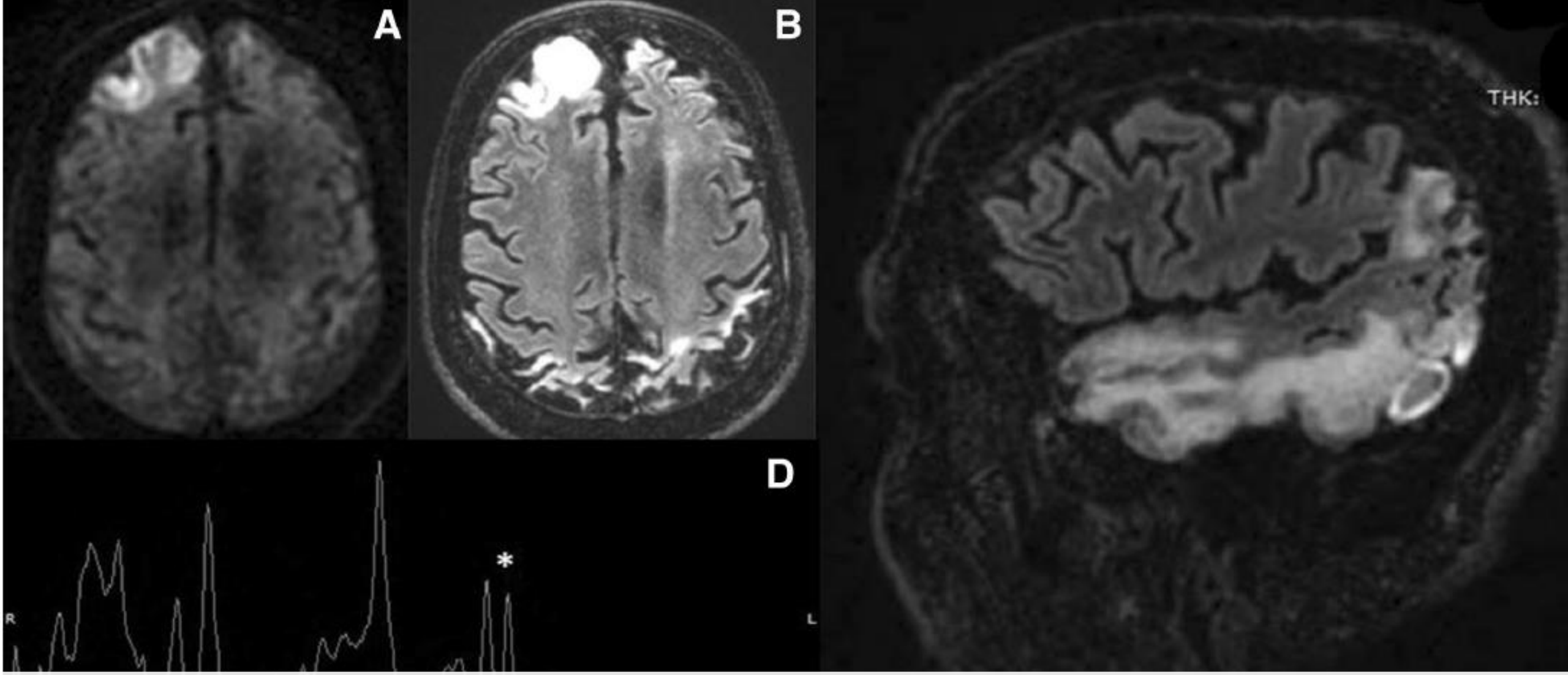


Fukutake et al, 2010, J Stroke Cerebrovasc Dis



Autosomal dominant SVD – HTRA1

- Autosomal dominant cases recent identified In Europe and Japan (Verdura et al, Brain 2015; Nozaki et al, Neurology 2016)
- Less severe course of disease than in CARASIL
  - Later age at onset of stroke and dementia
  - Lower frequency of non-neurological symptoms
  - 2md most common form of familial SVD in UK from WGS BRIDGE study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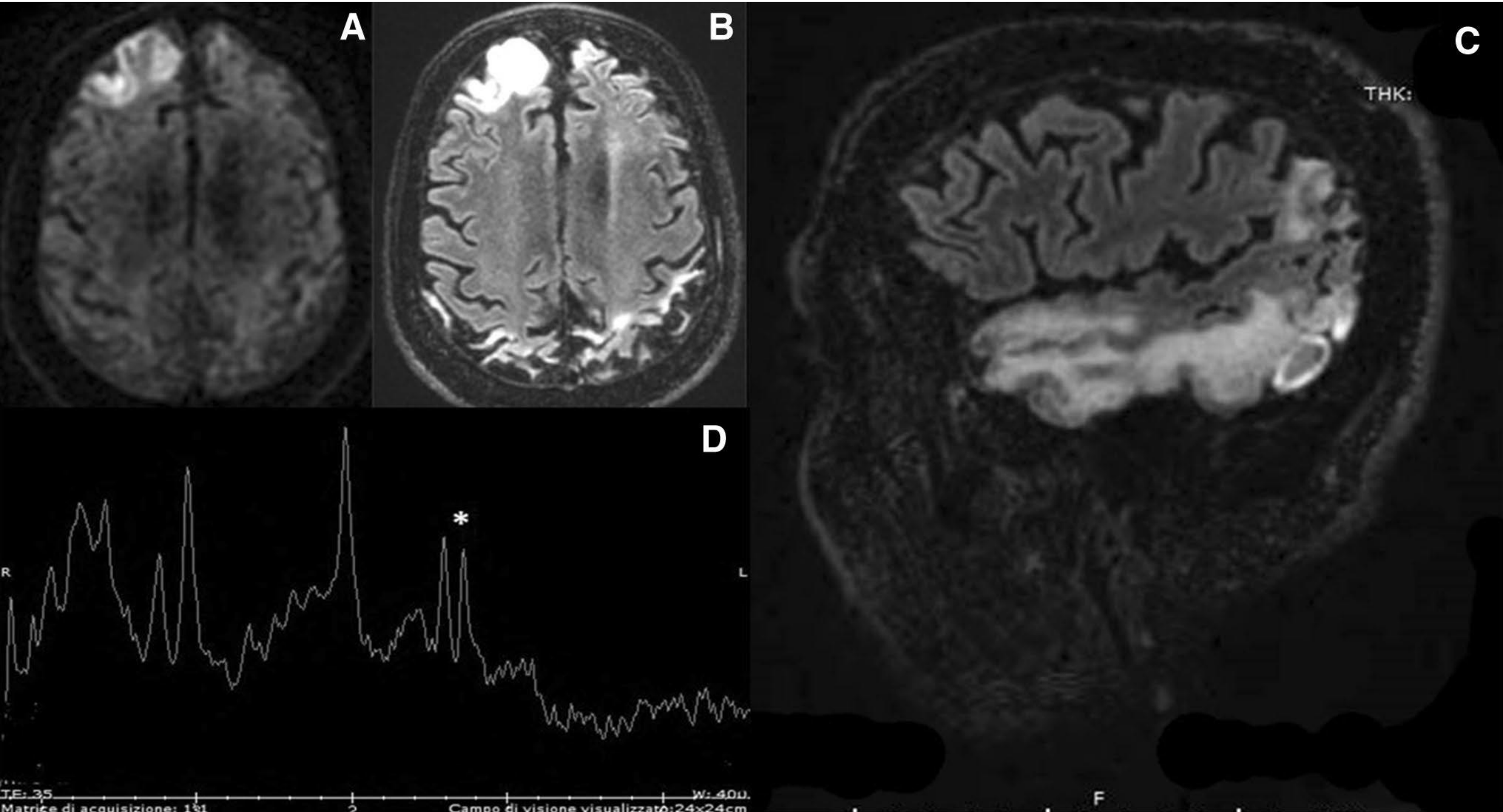
MELAS


TE: 35
W: 400
Matrice di acquisizione: 151
2
Campo di visione visualizzato: 24x24cm
F

MELAS

MITOCHONDRIAL ENCEPHALOMYOPATHY, LACTIC ACIDOSIS, AND **STROKE-LIKE** EPISODES

- A mitochondrial stroke-like episode is a subacute, evolving brain syndrome driven by seizure activity in genetically determined mitochondrial disease.
- These potentially treatable encephalopathic episodes can present at any age with neurological and/or psychiatric symptoms typically associated with cortical/subcortical MRI changes and EEG abnormalities.
- Stroke-like: **metabolic** stroke driven by SEIZURE activity !
- Recurrent stroke-like episodes: mostly posterior lesions
- **Mutation m.3243A>G tRNA Leu gene** but also other mt mutations and *POLG*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Matrice di acquisizione: 1
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Campo di visione visualizzato: 24x24cm
F

MANAGEMENT

- Fibrinolysis is not indicated to treat SLE
- Antiplatelet therapies are not indicated for secondary prevention of SLEs
- If an SLE is suspected and focal seizures are evident, they should be treated urgently with intravenous antiepileptic drugs, including levetiracetam, benzodiazepines or lacosamide.
- Valproic acid is contraindicated, mainly in patients with POLG variants
- We recommend midazolam as the first choice of general anaesthetics agent for treating refractory status epilepticus associated with SLE
- There is not enough evidence to support the use of intravenous L-arginine or citrulline to treat SLEs
- Even though there is no scientific evidence of positive impact of steroids in SLEs, their use is not contraindicated

Ng et al, 2020
Mancuso et al, 2020

COL4A1/2 α1 and α2 chains of COL4

- COL4A1,2 gene located on chromosome 13
- Autosomal dominant with variable penetrance
- COL4A1 mutations affecting collagne triple helix formation or stability have been associated with pathology
- Affects integrity of extracellular matrix
- ICH / ischaemic stroke
- cerebral microbleeds/ intracerebral aneurysms

Other manifestations include: intracerebral aneurysms, proteinuria, renal insufficiency, renal and hepatic cysts, tortuosities of retinal arteries, focal retinal haemorrhages, and early cataract

COL4A1/2 management
EAN consensus recommendations

- Antiplatelets and anticoagulants treatment are not recommended in *COL4A1/2* cSVD
- Intravenous thrombolysis is not recommended in a patient with a diagnosis of *COL4A1/2* cSVD
- Sporting activities with a high risk of head trauma, or excessive or prolonged exercise should be avoided in a patient with *COL4A1/2* cSVD
- A caesarean section should be considered in women giving birth where the foetus harbours a *COL4A1/2* variant

CONCLUSIONS

- Monogenic cSVD are rare but important diagnosis
- DIFFERENTIAL DIAGNOSIS between sporadic and monogenic SVD, even in the presence of vascular risk factors
- Growing prevalence due to the NGS technology
- There are increasing implications for common stroke (i.e. COL4 SNPs in sporadic SVD)
- CADASIL>HTRA1 AD>the others
- EAN consensus provides useful framework to guide diagnosis, differential diagnosis and management

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